

# Radioprotective and Radiosensitizing Effects of Sulfur-Containing Amino Acid Derivatives on Mice

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Z. Naturforsch. **35 c**, 726–728 (1980); received July 25, 1979/March 4, 1980

Radioprotector, Radiosensitizer, Sulfur Amino Acids, Hydantoins

Both protection and sensitization of Mice C57BL against  $^{60}\text{Co}$   $\gamma$ -rays by sulfur-containing amino acid derivatives – S-alkyl-L-cysteines, S-alkyl-2-methyl-DL-cysteines and their hydantoin derivatives, and sulfoxides of these compounds – were examined. DL-5-Allylthiomethyl-5-methylhydantoin (150 mg/kg body weight) had a remarkable radioprotective effect. The survival ratio was 4.33 or above two times as much as that of L-cysteine. On the other hand, its sulfoxide had a radiosensitizing effects; survival ratio, 0.333.

Since the discovery of chemical radiation protection [1, 2], many different kinds of sulfur compounds have been tested to find out their protective action on different biological systems [3]. Some very effective radioprotectors such as cysteamine, glutathione and so on which exhibit maximum protection when given in large doses are toxic to the mammals [4–8]. On the other hand, the exploration of radiosensitizer is also very important in the clinical cancer research [9–13].

So far we have been concerned with  $\gamma$ -radiolysis and UV-photolysis of sulfur-containing amino acids which occur in *Allium* plants such as onion and garlic in aqueous systems [14]. Furthermore, the radioprotective effect of these amino acid derivatives on *E. coli* has been examined [15]. The results indicated that the hydantoin derivatives of S-alkyl-cysteines were good radioprotectors on *E. coli*.

From a viewpoint of exploration of new radioprotectors and radiosensitizers on mammals, the effects of sulfur-containing amino acid derivatives on the survival of  $\gamma$ -irradiated mice were examined.

## Materials and Methods

Sulfur-containing amino acid derivatives shown in Fig. 1 were synthesized according to the previous reports [16–19]. Mice (C57BL, 5 weeks old male)

were subjected to 750 rad of  $\gamma$ -rays (dose rate, 46.4 rad/min) from  $^{60}\text{Co}$  in 30 min after a single intraperitoneal injection of 0.75 m mol/kg body weight of each compound. On 15 days and 30 days after irradiation, survived mice were counted.

## Results and Discussion

The radioprotective and radiosensitizing effects of sulfur-containing amino acid derivatives on mice were summarized in Table I. In the previous data [15], S-allyl compounds were more effective than S-

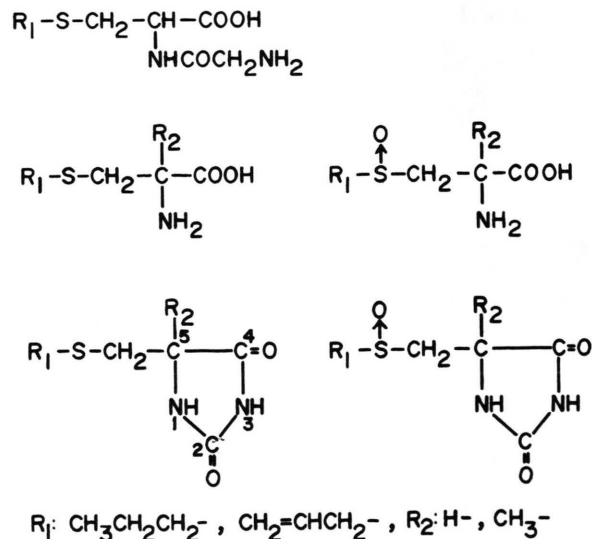


Fig. 1. General formulas of radioprotective and radiosensitizing sulfur-containing amino acid derivatives.

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0341-0382/80/0900-0726 \$ 01.00/0



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Table I. Effects of sulfur-containing amino acids and these derivatives on survivors of  $\gamma$ -irradiated mice.

No.	Compounds	750 rad $\gamma$ -irradiated mice survived (ratio)	
		15 days	30 days
1.	$\text{HS}-\text{CH}_2\underset{\text{NH}_2}{\text{CH}}\text{COOH}$	8 (0.889)	6 (2.00)
2.	$\text{CH}_2=\text{CHCH}_2-\text{S}-\underset{\text{NH}_2}{\text{CH}_2\text{CH}}\text{COOH}$	6 (0.669)	2 (0.667)
3.	$\text{CH}_3\text{CH}_2\text{CH}_2-\text{S}-\underset{\text{NH}_2}{\text{CH}_2\text{CH}}\text{COOH}$	7 (0.778)	4 (1.33)
4.	$\text{CH}_2=\text{CHCH}_2-\text{S}-\underset{\text{NHCOCH}_2\text{NH}_2}{\text{CH}_2\text{CH}}\text{COOH}$	8 (0.889)	5 (1.67)
5.	$\text{CH}_3\text{CH}_2\text{CH}_2-\text{S}-\underset{\text{NHCOCH}_2\text{NH}_2}{\text{CH}_2\text{CH}}\text{COOH}$	7 (0.778)	6 (2.00)
6.	$\text{HS}-\underset{\text{NH}}{\text{CH}_2}\underset{\text{NH}}{\text{CH}}-\underset{\text{O}}{\underset{\text{O}}{\text{C}}}=\text{O}$	10 (1.11)	10 (3.33)
7.	$\text{HS}-\text{CH}_2\text{CH}_2\text{NH}_2$	18 (2.00)	14 (4.67)
8.	$\text{CH}_2=\text{CHCH}_2-\text{S}-\underset{\text{NH}}{\text{CH}_2}\underset{\text{NH}}{\text{CH}}-\underset{\text{O}}{\underset{\text{O}}{\text{C}}}=\text{O}$	0 (0.00)	0 (0.00)
9.	$\text{CH}_2=\text{CHCH}_2-\text{S}-\underset{\text{NH}}{\underset{\text{NH}}{\text{CH}_2\text{C}}}\overset{\text{CH}_3}{\text{C}}-\underset{\text{O}}{\underset{\text{O}}{\text{C}}}=\text{O}$	19 (2.11)	13 (4.33)
10.	$\text{CH}_3\text{CH}_2\text{CH}_2-\text{S}-\underset{\text{NH}}{\underset{\text{NH}}{\text{CH}_2\text{C}}}\overset{\text{CH}_3}{\text{C}}-\underset{\text{O}}{\underset{\text{O}}{\text{C}}}=\text{O}$	20 (2.22)	14 (4.67)
11.	$\text{CH}_2=\text{CHCH}_2-\overset{\text{O}}{\underset{\text{O}}{\text{S}}}-\underset{\text{NH}_2}{\text{CH}_2\text{CH}}\text{COOH}$	6 (0.669)	3 (1.00)
12.	$\text{CH}_2=\text{CHCH}_2-\overset{\text{O}}{\underset{\text{O}}{\text{S}}}-\underset{\text{NH}}{\underset{\text{NH}}{\text{CH}_2\text{C}}}\overset{\text{CH}_3}{\text{C}}-\underset{\text{O}}{\underset{\text{O}}{\text{C}}}=\text{O}$	3 (0.333)	1 (0.333)
13.	no added <sup>a</sup>	9 (1.00)	3 (1.00)
14.	no irradiated <sup>b</sup>	20—	20—

<sup>a</sup> Irradiated without adding drugs. <sup>b</sup> No irradiated and no drugs added.

*n*-propyl compounds for radioprotection of *E. coli*. However, in the case of mice, the result was in reverse. Furthermore hydantoin derivatives were much more effective than original S-alkyl-L-cysteines. The most effective radioprotector which has been prepared by us is DL-5-*n*-propyl-thiomethyl-5-methylhydantoin (entry No. 10) as shown in Table I. The radioprotective effect of DL-5-*n*-propyl-thiomethyl-5-methylhydantoin was as large as that of cysteamine; survival ratio, 4.67. L-5-Allylthiomethylhydantoin (entry No. 8) was very toxic for mice; the injection of 0.75 mmol or 139.5 mg/kg body weight of the compound gave rise to 100% of death without  $\gamma$ -irradiation.

Sulfoxide amino acids such as S-allyl-L-cysteine sulfoxide (entry No. 11) which occur in garlic exhi-

bited radiosensitizing effect on *E. coli* [15], but they did not have any radiobiological effect on mice. On the other hand, DL-5-allylthiomethyl-5-methylhydantoin sulfoxide (entry No. 12) which is the hydantoin derivative of S-allyl-2-methyl-DL-cysteine sulfoxide exhibited significant radiosensitizing effect on mice; survival ratio 0.333. The injection of experimental dose of DL-5-allylthiomethyl-5-methylhydantoin sulfoxide (162.0 mg/kg body weight) did not decreased the survivals of mice at all.

It might be important to elucidate the correlation between  $\gamma$ -radiolysis mechanism of sulfur-containing compounds [20] and radioprotective or radiosensitizing action *in vivo*.

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